REMARKS/ARGUMENTS

Claims 58-62 are pending in this application. Applicants note and appreciate the withdrawal of the earlier objection to the specification and rejection under 35 U.S.C. §112, second paragraph.

The remaining rejections of claims 58-62 under 35 U.S.C. §§101 and 112, first paragraph are addressed below.

35 U.S.C. §§ 101 and 112, First Paragraph

The rejection of claims 58-62 for alleged lack of a credible, specific and substantial asserted utility or a well established utility, and for alleged lack of sufficient teaching for how to use the invention has been maintained from the previous Office Action.

In addressing Applicants' earlier arguments, the Examiner notes that "[n]o evidence has been submitted that it is the norm rather than the exception that protein levels are increased when gene amplification occurs in cancer." Therefore, the Examiner maintained the earlier position that in view of Pennica et al., Konopka et al., and Haynes et al., the skilled artisan would not assume a correlation between gene amplification and protein expression, "but would perform the experiment to verify it." From this the Examiner concludes that "it is not the norm that gene amplification, or even increased transcription, results in increased protein levels."

Applicants disagree, and respectfully traverse the rejection.

First of all, Applicants submit that Haynes et al. does not support the Examiner's position. Haynes et al. teaches that "**there was a general trend** but no strong correlation between protein [expression] and transcript levels" (Emphasis added). Haynes studied 80 *yeast* proteins to show that "protein levels cannot be **accurately** predicted from the level of the corresponding mRNA transcript" (Emphasis added) (see page 1863, paragraph 2.1, last line). For example, in Figure 1, there is a positive correlation between mRNA and protein amongst **most** of the 80 yeast proteins studied but the correlation is "not linear" and hence, "one cannot **accurately** predict protein levels from mRNA levels." In fact, very <u>few</u> data points deviated or scattered away from the expected normal or showed a lack of correlation between mRNA:

protein levels. Thus, contrary to the Examiner's reading, the Haynes data shows that it is more likely than not that a positive correlation exists between mRNA and protein levels.

Secondly, there are additional articles to show that generally, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. For example, Ornoft *et al.* (*Mol. and Cell. Proteomics*, 2002, Vol.1, pages 37-45, copy enclosed) studied transcript levels of 5600 genes in malignant bladder cancers many of which were linked to the gain or loss of chromosomal material using an array-based method. Ornoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (*Cancer Res.*, 2002, Vol. 62, pages 6240-45, copy enclosed) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (see page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.*, (*PNAS*, 2002, Vol. 99, pages 12963-12968, copy enclosed) who studied a series of primary human breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

Finally, enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about

30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology, that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.,* Hyman *et al.,* Pollack *et al.,* and the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO351 gene, that the PRO351 polypeptide is concomitantly overexpressed. Hence the antibodies specifically binding the PRO351 polypeptides have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use such antibodies for diagnosis of cancer.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejections.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further

issues outstanding, the Examiner is invited to contact the undersigned at the telephone number provided below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2630 P1C11**).

Respectfully submitted,

Date: July 28, 2004

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